REMARKS/ARGUMENTS

Claim 1 is active. Claim 1 defines A peptide homodimer of the following structure

Cys Tyr Thr Trp Asn Gln Met Asn Leu (SEQ ID NO: 44)

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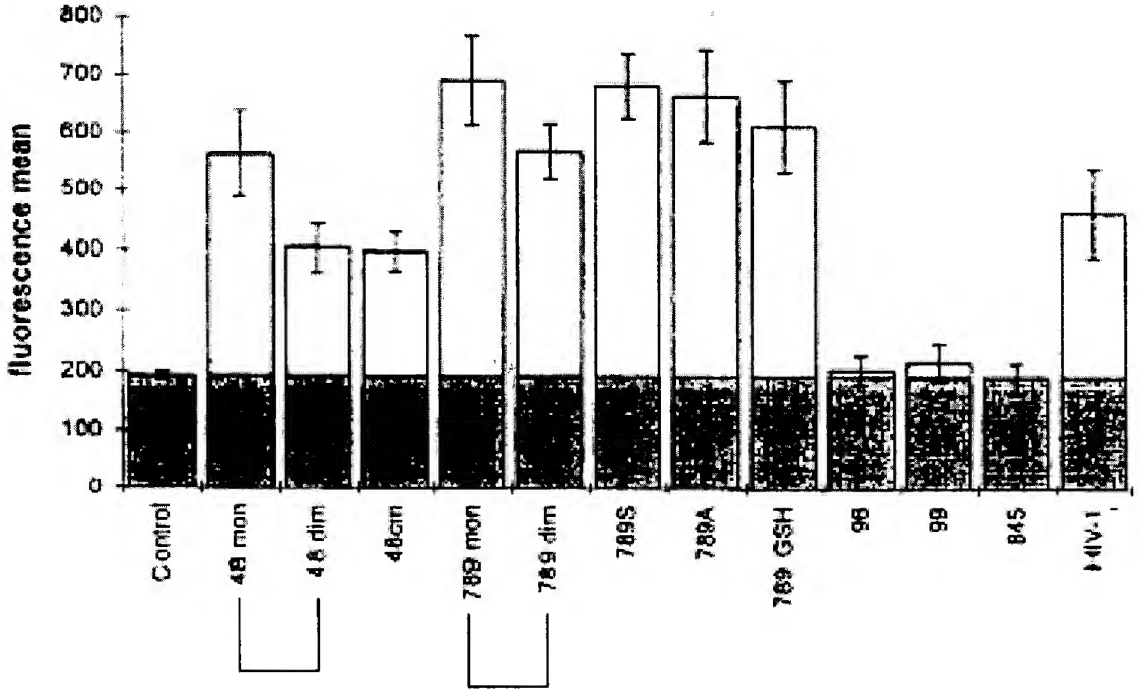
The obviousness rejection of Claim 1 as being unpatentable over EP 1371664 in view of Di Modugno is respectfully traversed.

EP '664 describes the monomer and Di Modugno is cited for the proposition that it would have been obvious to dimerize that monomer.

Di Modugno does not teach that homodimers can lead to increased anti- tumor immune response.

Di Modugno does not examine CTL-inducing activity. Di Modugno examines only binding affinity to HLA-A2. In Figure 2, the Office has inappropriately compared binding affinity of dimers 789 dim and 48 dim to control. In fact, the Office should have compared binding affinity of the dimers 789 dim and 48 dim to the monomers 48 mon and 789 mon.

Figure 2 of Di Modugno has been reproduced below with added emphasis lines at the bottom of the figure:



As can be seen in Figure 2, the monomer (48 mon) has a higher affinity than the dimer (48 dimer) and the monomer (789 mon) has a higher affinity than the dimer (789 dim). Accordingly, there would be no expectation of increased activity based on the increased binding affinities of the dimers when compared to the monomers, because the dimers have significantly reduced binding affinity as compared to the monomers.

Further, the Office, as described above, states "Di Modugno discloses the use of homodimers to form disulfide bonds in homodimers and that this increases the generation of different conformations..." and "In view of the binding and the view of the fact that applicant's claims are product claims, it is expected that the homodimers of the reference can induce CTL activity."

In the present case, given that the binding affinity of the homodimers is lower than the binding affinity of the monomers in Di Modugno, and given that as described by the Office and Di Modugno, the formation of homodimers through disulfide bonds "increases the

generation of different conformations," many of which would be expected to not be biologically active, it is not expected that "homodimers of the reference can induce CTL activity."

Indeed, Di Modugno, either alone or in combination with the other cited references, does not describe or suggest that CTL's induced by a homodimer could recognize and attach a cancer cell presenting the corresponding monomer, absent hindsight provided by the Applicant's disclosure.

Further, just because a compound binds to a receptor, there is no way, *a priori*, to predict if that compound will, for example, result in activating the receptor (e.g., be an agonist), partially activate the receptor (e.g., be a partial agonist), partially antagonize the receptor (e.g., be a partial antagonist), fully antagonize the receptor (e.g., be a full antagonist), act as both an antagonist and agonist (e.g., be a partial agonist/partial antagonist), or have no functional activity at all.

Applicants submit that the Office has failed to show why one of ordinary skill in the art would be able to expect that a peptide homodimer, that according to De Modugno has significantly less binding affinity than the monomer, and different and multiple confirmations, would induce CTL recognition of and cross-reactivity to the peptide monomer of the natural type. In short, there is an absence of linkage between binding activity and biological activity in the Office's argument.

Further, to show that "binding affinity for an HLA antigen" does not necessarily correspond to the "CTL-inducing activity", Applicants attach the publication of Parkhurst, *The Journal of Immunology*, 157 (6), pp. 2539-2548 (1996). Applicants also reference the Rule 1.132 Declaration dated May 14, 2008 submitted in US10/471,835.

Parkhurst demonstrates the independence of the "binding affinity for an HLA antigen" and the "CTL-inducing activity". Parkhurst et al. conducted amino acid substitution

for the purpose of improving CTL-inducing activity. Parkhurst et at states about cancer antigen peptides $G9_{209}$ and $G9_{280}$ as follows:

> many of the modified peptides bound with much greater affinity to HLA-A*0201 than the parent peptides (Tables II and III). However, many substitutions resulted in loss of recognition by gp100-reactive TIL, probably because conformational changes destroyed the TCR binding structure of the peptide/ MHC complex. (see p.2546, left column, line 19—22)

Thus, Parkhurst et al. clearly states that many of the modified peptides showed higher binding affinity to an HLA antigen than the wild-type (parent) peptides, but many of the modified peptides were not recognized by gp100-reactive TILs (tumor infiltrating lymphocytes).

Specifically, Table II and III at pages 2542 and 2543, respectively provide CTL inducing activity of several substituted types peptides having higher HLA-biding affinity than wildtype (parent) peptides ($G9_{209}$ and $G9_{280}$), said CTL-inducing activity being evaluated with the use of PBMCs from several patients. Table II and III clearly show that the "binding affinity for an HLA antigen" does not necessarily correlate to the "activity of induction CTL which recognize wild-type peptides." Similarly, $G9_{154}$ peptide is described as follows:

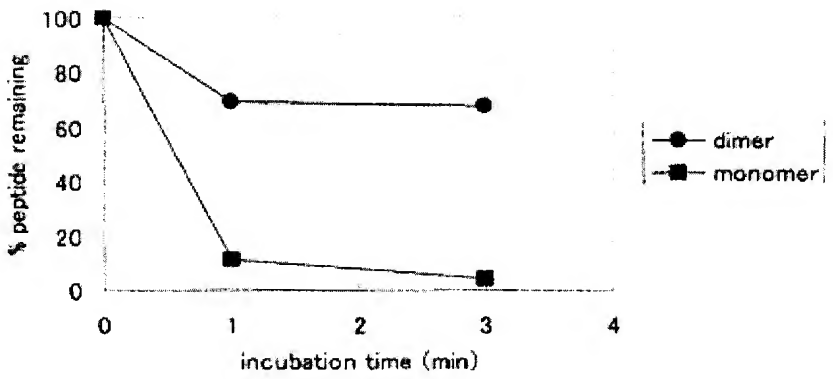
> no modified $G9_{154}$ peptide consistently induced $G9_{154}$ reactive CTL more efficiently than the parent peptide (data not shown) (See p2542, right column, the first full paragraph)

Thus, one of the ordinary skill in the art cannot expect whether the homodimer has CTL-inducing activity and, further, even if CTLs are induced, whether the induced CTLs recognize the wild peptides. Thus, the fact that a peptide has a binding affinity and that the peptide induces CTLs capable of recognizing a wild peptide are different stories.

The previously filed Rule 1.132 Declaration duly exemplified the superior effect of the claimed invention.

As described in the Declaration Under 37 C.F.R. § 1.132 filed on January 18, 2008, and executed by Dr. Haruo Sugiyama, M.D. Ph.D., in Experiment 2, pages 3 and 4 of the Declaration, monomer and homodimer of the peptide (SEQ ID NO: 44) were placed in mouse serum and the percentage of both monomer and homodimer remaining in the mouse serum was measured by reverse phase high performance liquid chromatography at the time of addition of the monomer and homodimer to the mouse serum, and at 1 and three minutes thereafter. The results of these measurements are presented in Figure 2 of the Declaration, reproduced below:

Figure 2



As can be seen in Figure 2, at both the 1 and 3 minute marks, the % of homodimer (e.g., dimer) remaining was significantly higher (at least 60% higher at 1 minute and approximately 60% higher at 3 minutes) than the % of monomer (e.g., monomer) remaining. Thus, the stability of homodimer in plasma was far superior to the stability of monomer.

Stability is blood / plasma is a very important property for a vaccine, and particularly for a cancer vaccine. Applicants submit this superior result of enhanced homodimer stability in blood / plasma is not described or suggested by any of ('564), ('664), Gaiger or Di Modungo, either alone or in combination. Based on the failure of ('564), ('664), Gaiger and

Di Modungo to describe or suggest enhanced homodimer stability in blood / plasma, this superior result is an unexpected result.

Applicants submit this superior and unexpected result is exactly the type of secondary consideration envisioned by the MPEP to address a *prima facie* case of obviousness. Withdrawal of the obviousness rejection is requested on this basis alone.

The obviousness rejection is respectfully traversed on the basis of a second superior and unexpected result.

As described in the Sugiyama Declaration at pages 2 and 3, the peptide dimer induced CTL's that recognized the natural type-peptide monomer. As described in Di Modugno, Summary, page 341, "Small peptides 8-10 amino acids long,...are usually presented and recognized by CD8+ cytolytic T lymphocytes (CTL's) associated with major histocompatability complex (MHC) class I molecules." Thus, a small 8-10 amino acid peptide forms a complex with an MHC Class I antigen and is thereby recognized by CTL's.

Applicants note, however, that dimers and monomers have different structures.

The Applicants discovered that CTL's induced by a dimer subsequently recognized a monomer; and, that CTL's induced by the dimer had a cross-reactivity and recognized the natural-type peptide monomer (underlining emphasis added). Applicants note that a peptide dimer would be expected to lack therapeutic activity if CTL's induced by administration of the peptide dimer did not recognize a peptide monomer, specifically a natural type peptide monomer, because cancel cells in a living body present a peptide monomer of the natural type.

Applicants respectfully submit the superior result that dimer induced CTL's recognition of and cross-reactivity to the peptide monomer of the natural type is not described or suggested by the cited references, either alone, or in combination. Accordingly, this superior result, based on the teachings of the cited references, is an unexpected result.

In short, the Rule 1. 132 declaration clearly show the CTL inducing activity and cross reactivity of the homodimer of the present invention. In addition, the Declaration also exemplified superior stability of the homodimer in the serum than the monomer. Stability in blood/plasma is a very important property for a vaccine, particularly for a cancer vaccine. Accordingly, the previously filed Rule 1.132 declaration duly exhibited an unexpectedly superior property of the claimed homodimer over the corresponding monomer.

Applicants request withdrawal of the obviousness rejection.

Applicants submit the present application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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